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Allan S. Hoffman

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CHRISTENSEN, O'CONNOR, JOHNSON, KINDNESS, PLLC  
1420 FIFTH AVENUE  
SUITE 2800  
SEATTLE, WA 98101-2347

EXAMINER

WESSENDORF, TERESA D

ART UNIT

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PAPER

**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

<b>Office Action Summary</b>	<b>Application No.</b> 09/755,701	<b>Applicant(s)</b> HOFFMAN ET AL.	
	<b>Examiner</b> TERESA WESSENDORF	<b>Art Unit</b> 1639	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

### Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

### Status

- 1) ☒ Responsive to communication(s) filed on 03 May 2008.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

### Disposition of Claims

- 4) ☒ Claim(s) 3,4,8,9,13-17,19,34-36 and 38-47 is/are pending in the application.
- 4a) Of the above claim(s) \_\_\_\_\_ is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 3,4,8,9,13-17,19,34-36 and 38, 40-41, 43--47 is/are rejected.
- 7) ☒ Claim(s) 39 and 42 is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

### Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on \_\_\_\_\_ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

### Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some \* c) ☐ None of:
- ☐ Certified copies of the priority documents have been received.
  - ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
  - ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\* See the attached detailed Office action for a list of the certified copies not received.

### Attachment(s)

- |  |   |
|--|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892)                     | 4) <input type="checkbox"/> Interview Summary (PTO-413)           |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | Paper No(s)/Mail Date. _____                                      |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08)          | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| Paper No(s)/Mail Date _____  | 6) <input type="checkbox"/> Other: _____                          |

**DETAILED ACTION**

***Status of the Claims***

Claims 3, 4, 8, 9, 13-17, 19, 34-36, and 38-47 are currently pending and examined on the merits.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior office action.

***Claim Rejections - 35 USC § 102/35 USC § 103***

Claims 3, 4, 8, 9, 13-15, 34-36, 38, 40, 41, and 43-47, as amended, are rejected under 35 U.S.C. 102(b) as anticipated by or, in the alternative, under 35 U.S.C. 103(a) as obvious over Davaran et al (Eur. Polym. J. 1998) as evidenced by Applicants' specification and Baroni et al (Eur. J. Biochem.) and Ito et al (Macromolecules 1992) and Theodore et al. (U.S. Patent No. 6,358,490) for reasons of record as reiterated below.

For claim 3, Davaran et al. teach the composition of claim 34, wherein the therapeutic, diagnostic, or prophylactic agent is a organic molecule (e.g., see abstract wherein ibuprofen is disclosed).

For claim 4, Davaran et al. teach the composition of claim 36, wherein the hydrophobic component is a synthetic vinyl-type hydrophobic polymer, naturally derived polymer, a membrane disruptive peptide, or a phospholipid bilayer disrupting agent

Art Unit: 1639

(e.g., see page 189, scheme 2 disclosing methacrylate "vinyl-type" polymer).

For claims 8 and 40, Davaran et al. teach the composition of claims 36 or 38, wherein the pH-sensitive linkage is an ester (e.g. see Davaran et al., page 190, column 2, paragraph 2 wherein PEG is connected to the methacrylate via an ester linkage).

For claim 9, Davaran et al. teach the composition of claim 34, wherein the therapeutic, diagnostic, or prophylactic agent is coupled to either the hydrophilic or the hydrophobic component by a degradable or disruptable linkage (e.g., see abstract wherein ibuprofen is connected via a hydrolysable thioester linkage; see also figures 1-3 showing hydrolysis rates).

For claim 13, Davaran et al. teach the composition of claim 36, wherein the conjugate further comprises a ligand, wherein the ligand specifically binds to a target molecule (e.g., see abstract wherein ibuprofen is disclosed). Davaran et al. do not explicitly state that ibuprofen is a ligand for a target but the Examiner contends that this is an inherent property of ibuprofen as exemplified by Baroni (e.g., see Baroni et al., page 6215, column 2, first full paragraph, "Ibuprofen binds to Sudlow's site II [on HSA] with  $K_d = 3.7 \times 10^{-7} \text{ M}$ ").

For claim 14, Davaran et al. teach the composition of claim 34, wherein the therapeutic, diagnostic, or prophylactic agent is complexed to a component of the conjugate (e.g., see scheme 2 and experiments).

For claim 15, Davaran et al. do not explicitly teach the composition of claim 36, wherein the pH sensitive linkage is hydrolyzed within about 30 to 60 minutes at a pH between 5.0 and 5.5. However, Davaran et al. discloses Applicants' preferred' ester linkage and, as a result, the Examiner contends that this would be an inherent property of the conjugate (e.g., see arguments for claim 36 below).

For claim 34, Davaran et al. teach the composition of claim 36 further comprising an agent, wherein the agent is a therapeutic, diagnostic, or prophylactic agent (e.g., see page 189, column 2, wherein a therapeutic drug is disclosed; see also abstract wherein ibuprofen is disclosed).

For claim 35, Davaran et al. teach the composition of claim 36, wherein the hydrophobic component comprises a synthetic polymer (e.g., see Davaran et al., page 189, scheme 2).

For claim 36, Davaran et al. teach hydrophilic copolymers prepared from acrylic type derivatives of ibuprofen containing hydrolysable thioester bonds (e.g., see Davaran et al., title and abstract), which anticipates the claimed invention. For

Art Unit: 1639

example, Davaran et al. teach a water-soluble hydrophilic conjugate having a hydrophobic component linked to a hydrophilic component by a pH-sensitive linkage (e.g., see Davaran et al., page 189, scheme 2 showing conjugate with methacrylate hydrophobic component; see also page 190, column 2, paragraph 2 wherein the water-soluble PEG is linked via a pH sensitive ester bond to the methacrylate). Please note that Davaran et al. do not explicitly state that the ester bond in the PEGM is a pH-sensitive linkage that is stable at a pH between 6.8 and 8 and hydrolyzed at a pH less than 6.5 but the Examiner contends that this is an inherent feature of the ester bond as exemplified by Applicants' specification and Theodore et al. (e.g., see specification, pages 22 and 23, especially page 23, first full paragraph disclosing ester as a "preferred" linkage with these properties; see also page 25, lines 9 and 10, "an ester or acetal bond, which is disrupted upon exposure to a stimulus, for example, a change in pH"; see also Theodore et al., column 22, last paragraph, "Ester and thioesters are hydrolytically cleaved under acidic or basic conditions [i.e., not neutral]" and thus would be cleaved at pH values less than 6.5).

When the reference discloses all the limitations of a claim except a property or function, and the examiner cannot determine whether or not the reference inherently possesses properties which anticipate or render obvious the claimed invention, "[T]he PTO can require an applicant to prove that the prior art

Art Unit: 1639

products do not necessarily or inherently possess the characteristics of his [or her] claimed product. Whether the rejection is based on inherency under 35 U.S.C. 102, on prima facie obviousness' under 35 U.S.C. 103, jointly or alternatively, the burden of proof is the same... [footnote omitted]." The burden of proof is similar to that required with respect to product-by-process claims. In re Fitzgerald, 619 F.2d 67, 205 USPQ 594 (CCPA 1980) (a case indicating that the burden of proof can be shifted to the applicant to show that the subject matter of the prior art does not possess the characteristic relied on whether the rejection is based on inherency under 35 U.S.C. § 102 or obviousness under 35 U.S.C. § 103). See MPEP §§ 2112- 2112.02.

Please also note that the amount of cleavage is not specified in the claims, nor are the conditions under which such cleavage occurs. Thus, the claims read on minimal cleavage under extreme conditions of temperature, pressure, pH, etc. In addition, cleaving the conjugate at this ester bond would release the hydrophobic component (i.e., the acrylic "vinyl type" polymer) from the hydrophilic component (i.e., the PEG). Davaran et al. do not explicitly state that the hydrophobic component will disrupt a membrane when released from the hydrophilic conjugate but the Examiner contends that this is intended use language and thus should not be afforded any patentable weight or, alternatively, is inherently disclosed by the reference since the hydrophobic polymer possesses the same vinyl methacrylate structure as that currently claimed by Applicants and, in addition, Ito et al. state that PMMA, like the one disclosed by Davaran, disrupts PC membranes (e.g., see

Art Unit: 1639

claims 39, 46, and 47; see especially page 11, lines 24 and 25, "Random, block and graft copolymers that include acrylate groups and alkyl substituted acrylate groups are preferred."; see also Ito et al., figure 4 showing pH reversible disruption; see also figure 5; see also figure 6 showing increase in disruption with increase in salt concentration; see also figure 7 comparing PMAA to PEAA). "When the PTO shows a sound basis for believing that the products of the applicant and the prior art are the same, the applicant has the burden of showing that they are not." In re Spada, 911 F.2d 705,709, 15 USPQ2d 1655, 1658 (Fed. Cir. 1990). The Office does not have the facilities to make such a comparison and the burden is on the applicants to establish the difference. See In re Best, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977) and Ex parte Gray, 10 USPQ 2d 1922 1923 (PTO Bd. Pat. App. & Int.). See also MPEP § 2112- 2112.02. Please also note that the amount of disruption is not specified in the claims, nor are the conditions under which such disruption occurs. Thus, the claims read on minimal disruption under extreme conditions of temperature, pressure, etc. For claim 38, Davaran et al. teach a water-soluble conjugate comprising i) a hydrophobic synthetic vinyl-type polymer (e.g., see Davaran et al., page 189, showing methacrylate polymer; see also page 190, column 2, paragraph 2 disclosing use of water- soluble PEGM). Davaran et al. do not

Art Unit: 1639

explicitly state that the polymer is an endosomal membrane disruptive when released from the hydrophilic conjugate but the Examiner contends that this is intended use language and thus should not be afforded any patentable weight or, alternatively, is inherently disclosed by the reference since the hydrophobic polymer possesses the same vinyl methacrylate structure as that currently claimed by Applicants and Ito et al. disclose a similar pH dependent disruption to that of Applicants' preferred PEAA (e.g., see claims 39, 46, and 47; see especially page 11, lines 24 and 25, "Random, block and graft copolymers that include acrylate groups and alkyl substituted acrylate groups are preferred."; see also Ito et al., figures 3-7, especially figure 7). "When the PTO shows a sound basis for believing that the products of the applicant and the prior art are the same, the applicant has the burden of showing that they are not." In re Spada, 911 F.2d 705, 709, 15 USPQ2d 1655, 1658 (Fed. Cir. 1990). The Office does not have the facilities to make such a comparison and the burden is on the applicants to establish the difference. See In re Best, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977) and Exparte Gray, 10 USPQ 2d 1922 1923 (PTO Bd. Pat. App. & Int.). See also MPEP § 2112- 2112.02. Please also note that the amount of disruption is not specified in the claims, nor are the conditions under which such disruption occurs. Thus, the

Art Unit: 1639

claims read on minimal disruption under extreme conditions of temperature, pressure, etc. Davaran et al. also disclose (b) a plurality of pendant hydrophilic polyalkylene oxide components (e.g., see scheme 2 and page 190, column 2, paragraph 2 wherein a plurality of PEGs are incorporated into the conjugate via the PEGMs). Finally, Davaran et al. disclose (e) a plurality of pH-sensitive linkages (e.g., see scheme and page 190, column 2, paragraph 2 wherein the plurality of PEGs are attached via an ester linkage). Again, Davaran et al. do not explicitly state that each of the pendant polyalkylene oxide components are covalently linked to the polymer through a pH-sensitive linkage that is stable at a pH between 6.8 and 8 and hydrolyzed at a pH less than 6.5. However, the Examiner contends that this is an inherent feature of the ester bond as exemplified by Applicants' specification and Theodore et al. (e.g., see specification, pages 22 and 23, especially page " 23, first full paragraph disclosing ester as a "preferred" linkage with these properties; see also page 25, lines 9 and 10, "an ester or acetal bond, which is disrupted upon exposure to a stimulus, for example, a change in pH"; see also Theodore et al., column 22, last paragraph, "Ester and thioesters are hydrolytically cleaved under acidic or basic conditions [i.e., not neutral]" and thus would be cleaved at pH values less than 6.5). When the reference discloses all the

Art Unit: 1639

limitations of a claim except a property or function, and the examiner cannot determine whether or not the reference inherently possesses properties which anticipate or render obvious the claimed invention, "[T]he PTO can require an applicant to prove that the prior art products do not necessarily or inherently possess the characteristics of his [or her] claimed product. See MPEP §§ 2112- 2112.02. Please also note that the amount of cleavage is not specified in the claims, nor ' are the conditions under which such cleavage occurs. Thus, the claims read on minimal cleavage under extreme conditions of temperature, pressure, etc. for extended periods of time.. For claim 41, Davaran et al. teach in addition to the limitations set forth in claim 38 use of a therapeutic or diagnostic agent such as ibuprofen (e.g., see Davaran et al., abstract).

For claim 43, Davaran et al. teach the composition of claim 41, wherein the pH- sensitive linkage is selected from the group consisting of... an ester (e.g., see Davaran et al., page 190, Column 2, paragraph 2 wherein PEG is connected to the methacrylate via an ester linkage). For claim 44, Davaran et al. teach the composition of claim 41, wherein the therapeutic or diagnostic agent is selected from the group consisting of a protein ... an organic molecule (e.g., see abstract wherein ibuprofen is disclosed).

For claim 45, Davaran et al. teach the composition of claim 36, wherein the hydrophobic component comprises a random, block, or graft copolymer, wherein the copolymer comprises an alkyl substituted or unsubstituted acrylate group (e.g., see scheme 2 wherein methacrylate is disclosed). For claim 46, Davaran et al. teach the composition of claim 36, wherein the hydrophobic component comprises poly(ethylacrylic acid), poly(propylacrylic acid), poly(butylacrylic acid), or acrylic acid polymer and copolymers (e.g., see scheme 2 wherein methacrylate is disclosed). For claim 47, Davaran et al. teach a composition for enhancing transport through a membrane, comprising a hydrophilic conjugated having a hydrophobic component linked to a hydrophilic component by a pH-sensitive linkage (e.g., see scheme 2 and page 190, column 2, paragraph) wherein a hydrophobic methacrylate polymer is linked via a pH-sensitive linkage to a hydrophilic PEG). Davaran et al. do not explicitly state that the pH-sensitive linkage is stable at a pH between 6.8 and 8 and hydrolyzed at a pH less than 6.5 to release the hydrophobic component, but the Examiner contends that this is an inherent feature of the ester bond as exemplified by Applicants' specification and Theodore et al. (e.g., see specification, pages 22 and 23, especially page 23, first full paragraph disclosing ester as a "preferred" linkage

Art Unit: 1639

with these properties; see also page 25, lines 9 and 10, "an ester or acetal bond, which is disrupted upon exposure to a stimulus, for example, a change in pH"; see also Theodore et al., column 22, last paragraph, "Ester and thioesters are hydrolytically cleaved under acidic or basic conditions [i.e., not neutral]" and thus would be cleaved at pH values less than 6.5). [See the case law cited above and MPEP §§ 2112- 2112.02 for inherency rejections]. Please also note that the amount of cleavage is not specified in the claims, nor are the conditions under which such cleavage occurs. Thus, the claims read on minimal cleavage under extreme conditions of temperature, pressure, etc. for extended periods of time. In addition, Davaran et al. disclose a hydrophilic component comprises a polyalkylene oxide (e.g., PEG, see above) and a hydrophobic component comprises a random, block, or graft copolymer, wherein the copolymer comprises an alkyl substituted or unsubstituted acrylate group (e.g., see scheme 2, wherein methacrylate polymer is disclosed). Finally, Davaran et al. do not explicitly state that the hydrophobic component is membrane disruptive and allows enhanced transport through a membrane when released from the hydrophilic conjugate but the Examiner contends again that this is intended use language and thus should not be afforded any patentable weight or, alternatively, is inherently disclosed by

Art Unit: 1639

the reference since the hydrophobic polymer possesses the same vinyl methacrylate structure as that currently claimed by Applicants and Ito et al. expressly state that PMAA, like the one disclosed by Davaran et al., can disrupt membranes (e.g., see claims 39, 46, and 47; see especially page 11, lines 24 and 25, "Random, block and graft copolymers that include acrylate groups and alkyl substituted acrylate groups are preferred."; see also Ito et al., figures 3-7; especially figure 7). See also MPEP § 2112-2112.02. Please also note that the amount of disruption is not specified in the claims, nor are the conditions under which such disruption occurs. Thus, the claims read on minimal disruption under extreme conditions of temperature, pressure, etc.

### ***Response to Arguments***

Applicants submit that the independent claims' recitation that the hydrophobic component is endosomal membrane disruptive is not an intended use, but rather an element of the claim that must be afforded patentable weight. According to M.P.E.P. 2111.02 II, whether a statement recites the purpose or intended use must be decided by whether the recited purpose or intended use results in a structural difference between the claimed invention and the prior art. When the recited purpose or intended use results in a structural difference between the

Art Unit: 1639

claimed invention and the prior art, the recitation serves to limit the claim. See, e.g., *In re Otto*, 312 F.2d 937, 938, 136 U.S.P.Q. 458, 459 (CCPA 1963). The claimed invention requires that the hydrophobic component is endosomal membrane disruptive. The recitation leads to specific structural requirement on the hydrophobic component of the claimed conjugate. For example, as evidenced by the specification, in order to be endosomal membrane disruptive, the carboxylic acid group-containing polymer serving as the hydrophobic component in the claimed conjugate must be in a sufficiently protonated form at the pH in the endosomes (between 5.0 and 6.5). This requirement imparts a structural limitation to the carboxylic acid-containing polymer useful as the hydrophobic component in the claimed conjugate. Therefore, the "endosomal membrane disruptive" recitation provides a structural limitation and must be afforded patentable weight.

In reply, applicants' arguments that the claimed hydrophobic component requires the structural limitation to the carboxylic-acid containing polymer are not commensurate in scope with the claims. The claims do not positively recite a structural carboxylic acid-containing polymer responsible for said function. While the specification recites the argued limitation, however, claim 36, at least, does not recite the

Art Unit: 1639

carboxylic structure. Though understanding the claim language may be aided by explanations contained in the written description, it is important not to import into a claim limitations that are not part of the claim. For example, a particular embodiment appearing in the written description may not be read into a claim when the claim language is broader than the embodiment. *Superguide Corp. v. DirecTV Enterprises, Inc.*, 358 F.3d 870, 875, 69 USPQ2d 1865, 1868 (Fed. Cir. 2004). MPEP 2111.01(II). Be as it may, Davaran recites a methacrylic acid (i.e., a carboxylic-containing acid. Note applicants' statement below for said poly(methacrylic acid)).

Applicants submit that the cited references fail to teach or suggest a composition that includes each and every element of the claimed invention. Specifically, the cited references fail to disclose a hydrophobic component that is endosomal membrane disruptive when released from the conjugate. The Davaran reference describes hydrophilic copolymers that include ibuprofen. The copolymers are prepared by copolymerization of a drug containing monomer (S-methacryloyloxyethyl-co-methyl-4-(2-methylpropyl)benzenethioacetate (MOETE)) and a comonomer including methacrylic acid (polyethylene glycol methacrylate). See page 188, first full paragraph, and Scheme 2 at page 189. Therefore, the Davaran reference discloses a copolymer with the

Art Unit: 1639

following structure in which the hydrophilic component is a PEG moiety and the hydrophobic component includes a poly(methacrylic acid) moiety. Hydrolysis of the ester linkage intermediate the PEG group and the poly(methacrylate) backbone in Davaran's conjugate do not provide a hydrophobic component (i.e., vinyl polymer) that is endosomal membrane disruptive. Hydrolysis of Davaran's conjugate yields a poly(methacrylic acid). According to the specification, the hydrophobic component of the claimed invention is not hydrophobic at physiological pH, typically in the range of between 6.8 and 7.5, and approximately 7.4 inside cells, but becomes hydrophobic at the pH inside the endosomes (between 5.0 and 6.5) (page 10, lines 25-28). In order to be endosomal membrane disruptive, the specification states that the pKa for carboxylic acid groups on the hydrophobic component are such that they tend to be protonated at the pH range present in endosome, i.e., between 5.0 and 6.5 (page 11, lines 1-3). Therefore, the endosomal membrane disruptive ability relates to the hydrophobicity of the polymer at endosomal pH, which is affected by the combined effect of the factors including the alkyl groups of the polymer and the pKa of carboxylic acid groups of the polymer. This combined effect leads to the differences in behavior for poly(methacrylic acid), poly(ethylacrylic acid), and poly(propylacrylic acid).

In reply, much of applicants' arguments, as stated above, are not commensurate in scope with the claims. Furthermore, it is well known in the art and as can be gleamed from applicants' arguments and disclosure, endosomal membrane disruptive is a function attributable to the type of the polymer. The art has recognized this problem. Accordingly, the art has shown that it would be within the ordinary skill in the art to pick and choose different polymers from the ones that are known and available to have said function of lysing endosomal membrane. Such lysing or disruption enables entry of the drug e.g., antisense to the intended site. Endosomal disruption, including the pH adjustment and controlled degradation, are multi-functions attributable to the carrier polymer having said functions.

Applicants state that the Declaration of Patrick Stayton submitted with the response filed October 31, 2007, evidences the differences in behavior for poly(methacrylic acid), poly(ethylacrylic acid), and poly(propylacrylic acid). Unlike higher alkyl poly(alkylacrylic acids), poly(methacrylic acid) is insufficiently hydrophobic to be endosomal membrane disruptive. Therefore, while poly(ethylacrylic acid) and poly(propylacrylic acid) are effective in endosomal membrane disruption, poly(methacrylic acid), which is a component of the Davaran conjugate, is not. Furthermore, there is no apparent reason to

Art Unit: 1639

modify Davaran's teaching to arrive at the claimed invention.

The Davaran reference discloses polymeric-drug conjugates for delivering ibuprofen to solve the drug's irritant side effects on the gastro-enteric mucosa and its poor water solubility.

Hydrophilic comonomers, such as methacrylic acid, methacrylamide, vinyl imidazole, and polyethylene glycol methacrylate, were used to copolymerize with MOETE to solubilize the drug. According to Davaran, the copolymers obtained showed water solubility sufficient for homogeneous hydrolysis of the polymeric-drug conjugates disclosed in the reference (page 190, right column). Applicants further submit that it is well known to the skilled person to use polyethylene glycol methacrylate (PEGM) as a solubilizer for hydrophobic drugs or polymers. See, for example, page 190, right column, of the Davaran reference. Because the problem associated with the solubility of the polymeric prodrug has been satisfactorily solved by using the disclosed hydrophilic comonomers and further because polyethylene glycol methacrylate (PEGM) is well-known in the field of art as a solution for solubilizing hydrophobic drugs or polymers, there is no apparent reason to modify Davaran's teaching to arrive at the claimed invention.

In reply, in considering disclosure of a reference, it is proper to take into account not only specific teachings of the reference but also **inferences** which one skilled in the art would reasonably be expected to draw therefrom. In re Preda, 159 USPQ 342; In re DeLise 160 USPQ 806. Thus, applicants' arguments that poly(methacrylic acid) is **insufficiently** hydrophobic to be endosomal membrane disruptive suggests that at least it is an endosomal membrane disruptive albeit not of greater effect as the higher homologs alkyl poly(alkylacrylic acids). See applicants' arguments above that the disruptive effect is due to the presence of alkyl groups and carboxylic groups. Furthermore, the showing in the declaration drawn to the effects of the three polymers is not a showing commensurate in scope with the claims. In showing "unexpected results" applicants must establish that there actually is a difference between the results obtained through the claimed invention and those of the prior art, that the difference actually obtained would not have been expected by one skilled in the art at the time of the invention, and that the difference is of practical advantage. Compare In re Freeman, 474 F.2d 1318, 177 USPQ 139 (CCPA 1973), In re Klosak, 455 F.2d 1077, 173 USPQ 14 (CCPA 1972) and In re D'Ancicco, 452 F.2d 1060, 172 USPQ 241. Moreover, as shown by the prior art the conjugate composition is known in the art. It would be within the ordinary skill in the art to determine the polymers' function. The art has long recognized that in order for a

Art Unit: 1639

polymer carrier to successfully deliver a drug to the intended site it must be multifunctional as stated above, i.e., to be able to transfect the gene by lysing the membrane like the endosomal membrane.

Applicants argue that the Ito reference does not teach poly(methacrylic acid) to be endosomal membrane disruptive. The Examiner has relied on the Ito reference for the teaching that poly(methacrylic acid) disrupts polycarbonate (PC) membranes. The Ito reference discloses straight-pored polycarbonate (PC) membranes with surface grafted poly(acrylic acid), poly(methacrylic acid), and poly(ethylacrylic acid). The graft polymeric chains affect the closure of the pores of the membrane. The dissociation of the polymeric graft changes with the pH of water, which leads to the pH response of the water permeation rate through the membrane. Nowhere does the Ito reference disclose any polymer that is membrane disruptive. In addition, nowhere does the Ito reference disclose an endosomal membrane. The only membrane disclosed by the Ito reference is a polycarbonate membrane, which is neither a biological membrane nor an endosomal membrane, as recited in the claimed invention.

In reply, the implicit disclosure of Ito would suffice the finding of obviousness. Ito's disclosure that the dissociation

of the polymeric graft changes with the pH of water would lead one to the claimed endosomal disruption. Ito positively teaches the above argued higher polymeric compounds causing endosomal disruptive membrane. See applicants' arguments above and the declaration with respect to the higher alkyl polymer groups' effectiveness in disrupting endosomal membrane. The test for combining references is not what the individual references themselves suggest but rather what the combination of the disclosures taken as a whole would suggest to one of ordinary skill in the art. In re McLaughlin, 170 USPQ 209 CCPA 1971. The court must approach the issue of patentability in terms of what would have been obvious to one of ordinary skill in the art at the time the invention was made in view of the sum of all the relevant teachings in the art, not in view of the first one and then another of the isolated teachings in the art. In re Kuderna, 165 USPQ 575 CCPA 1970. "[t]he Court recognized that when a patent claims a structure already known in the prior art that is altered by the mere substitution of one element for another known in the field, the combination must do more than yield a predictable result." KSR International Co. v. Teleflex Inc., 550 USPQ2d 1385 (2007) 2141 to 2145.

Claims 3, 4, 8, 9, 13-17, 19, 34-36, 38, 40, 41, and 43-47 have been rejected under 35 U.S.C. § 103(a) as being unpatentable over the teachings of the Davaran reference in view

Art Unit: 1639

of U.S. Patent No. 4,571,400, issued to Arnold, and Vinogradov et al, as evidenced by the present application, the Baroni reference, the Ito reference, and the Theodore reference.

Applicants argue that the Arnold reference is directed to pharmaceutical compositions containing dihydrocodeine or a pharmaceutically acceptable acid addition salt thereof and ibuprofen or a pharmaceutically acceptable salt thereof that are useful in treating pain. The reference discloses a wide range of pharmaceutically acceptable carriers for use with ibuprofen. Because neither the Vinogradov reference nor the Arnold reference discloses a polymer that is endosomal membrane disruptive at endosomal pH, the deficiencies of the teachings of the Davaran, Baroni, Ito, and Theodore references noted above with regard to independent Claims 36, 38, 41, and 47 are not cured by the teachings of the Vinogradov and Arnold references.

In reply, for the reasons stated above, the combined teachings of the prior art would lead one having ordinary skill in the art to claimed known composition. It would be within the ordinary skill in the art at the time the invention was made to determine whether the polymer used as e.g., transfection carrier would have one of the desired and known function of endosomal membrane disruption/lyses. As stated by applicants above this is a function inherent to the carboxylic acid containing polymer.

Claims 39 and 42 are free of prior art and objected to as being dependent upon the rejected claims as given above.

No claim is allowed.

### **Conclusion**

Applicant's amendment necessitated the new [ground(s)] arguments presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to TERESA WESSENDORF whose telephone number is (571)272-0812. The examiner can normally be reached on flexitime.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James Schultz can be reached on 571-272-0763. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.


Application/Control Number: 09/755,701

Page 24

Art Unit: 1639

/TERESA WESSENDORF/

Primary Examiner, Art Unit 1639

<div>Application Number</div> <div></div>	Application/Control No.	Applicant(s)/Patent under Reexamination	
	09/755,701	HOFFMAN ET AL.	
	Examiner	Art Unit	
	TERESA WESSENDORF	1639	